BMC Infectious Diseases

RESEARCH

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The risk of hepatitis B virus reactivation in COVID-19 patients treated with corticosteroids: a retrospective observational cohort study

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Abstract

Background Systemic corticosteroids, recommended for adult patients with coronavirus disease 2019 (COVID-19) who require supplemental oxygen, may carry an increased risk of reactivating latent infections such as hepatitis B virus (HBV) infection.

Methods This retrospective observational cohort study of prospectively collected clinical data evaluated HBV screening frequency and examined the prevalence and reactivation of HBV among hospitalised adults treated with systemic corticosteroids for COVID-19 at a tertiary care hospital in Slovenia.

Results Anti-HBc screening was conducted in 1,793/2,134 (84%) hospitalised patients receiving corticosteroids for COVID-19 (median age 70 years [IQR 59–79 years]; 1,082 [60.3%] were male). Among the 1,793 screened patients, 157 (8.8%) were anti-HBc positive, and 5 (0.3%) of them also HBsAg positive. All five HBsAg-positive patients were aviremic. HBV infection was previously known in three of these patients (two on long-term tenofovir treatment) and identified *de novo* in two. Entecavir was initiated for one patient. Throughout the hospitalisations and 12-month follow-up periods, no cases of HBV viral rebound were observed in any of the HBsAg positive patients; one of the treated patients succumbed to COVID-19 pneumonia. No HBV reactivation or unexplained hepatopathy occurred in the 152 anti-HBc positive/HBsAg negative patients, none of whom were given antiviral prophylaxis.

Conclusions Corticosteroids for COVID-19 did not appear to be a significant risk factor for HBV reactivation in cases of occult hepatitis B. Universal antiviral prophylaxis in HBsAg negative/anti HBc positive individuals may not be warranted with short courses of corticosteroids for COVID-19 in the absence of other risk factors for HBV reactivation.

Trial registration Retrospectively registered with ClinicalTrials.gov, NCT07154212, September 2, 2025.

Keywords Hepatitis B virus, Reactivation, COVID-19, Corticosteroids

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Introduction

Since July 2020, systemic corticosteroids, preferably dexamethasone at a dosage of 6 mg once daily for up to 10 days, have been recommended for hospitalised adult patients with coronavirus disease 2019 (COVID-19) who require supplemental oxygen [1]. However, COVID-19 treatment guidelines caution that systemic corticosteroids may be associated with adverse effects, including an increased risk of reactivation of latent infections such as hepatitis B virus (HBV). While guidelines acknowledge this risk, they lack specific recommendations regarding risk stratification, monitoring, or managing HBV infection in patients undergoing corticosteroid treatment for COVID-19 [1, 2]. Research estimates that the risk of HBV reactivation in anti-HBc positive patients receiving high doses of corticosteroids (greater than 20 mg prednisone daily or equivalent) for four or more weeks is substantial, with rates exceeding 10% in HBsAg positive patients, and between 1% and 10% in HBsAg negative patients. Conversely, the risk of HBV reactivation in patients on systemic prednisone equivalent < 10 mg daily in HBsAg or HBV DNA positive patients or < 40 mg daily for less than one week in HBsAg and HBV DNA negative patients is low (below 1%). However, the potential for reactivation with 40 mg daily of prednisone equivalent administered for one to four weeks remains uncertain [3–5]. To prevent HBV reactivation, the European Association for the Study of the Liver (EASL) recommend considering antiviral therapy for patients with chronic, occult, or resolved HBV who are treated for COVID-19 with corticosteroids or other immunosuppressants [6]. Following this guidance, anti-HBc screening for all patients undergoing corticosteroid therapy for COVID-19 was recommended at our institution, with reflex HBsAg testing in anti-HBc positive cases, and antiviral prophylaxis for individuals with detectable HBV DNA. Slovenia is a Central European country with an estimated HBV prevalence of 0.5% [7] and low HBV vaccination coverage for those born before 1992 [8]. Understanding HBV management during corticosteroid treatment is crucial. This retrospective observational cohort study of prospectively collected clinical data aimed to evaluate adherence to HBV screening guidelines in a country characterized by low HBV prevalence and assess the potential for reactivation of HBV infection in anti-HBc positive patients receiving corticosteroids for COVID-19.

Methods

Design and setting

The study conducted at the University Medical Centre Ljubljana, Slovenia, included adult patients (aged 18 years and above) hospitalised with COVID-19 from November 1, 2020, to March 31, 2021 (SARS-CoV-2 wild-type period); from October 1 to November 23, 2021 (Delta period); and from January 15 to April 8, 2022 (Omicron period). Demographic, clinical, and laboratory data for patients hospitalised due to COVID-19 and receiving systemic corticosteroid treatment during the hospital stay were collected at hospital discharge and at ≥ 3 months after completing corticosteroid treatment and analysed from June 1 to August 31, 2024. Study results were reported according to STROBE guidelines for observational studies.

Participants

Eligibility for inclusion was determined through the electronic medical record. Patients were considered eligible if they had a positive SARS-CoV-2 RNA PCR test either within ten days before admission or during their hospital stay. Those presenting with clinical symptoms consistent with acute COVID-19, such as fever, cough, dyspnoea, and pneumonic infiltrates on chest X-ray, were classified as COVID-19 cases. COVID-19 patients who received systemic corticosteroids for COVID-19 pneumonia requiring supplemental oxygen were further analysed for HBV screening. Systemic corticosteroids for COVID-19 were either dexamethasone 6 mg daily or an equivalent dose of other corticosteroids or high dose methylprednisolone 1 mg/kg daily for up to 10 days. Patients who were hospitalised for medical conditions unrelated to COVID-19 or who received corticosteroid therapy for non-COVID-19 reasons were excluded. Critically severe COVID-19 was defined as progression to invasive mechanical ventilation or death, correlating with levels 7, 8, 9, and 10 of the World Health Organization's COVID-19 Clinical Progression Scale [9]. Progression of HBV infection was assessed by testing transaminases activity in anti-HBc positive/HBsAg negative patients and additionally by testing serum HBV DNA in HBsAg positive patients and those anti-HBc positive/HBsAg negative patients with transaminitis (elevated transaminases). HBV reactivation in HBsAg positive patients was defined as HBV DNA increase ≥ 2 $\log_{10}$ from a pre-corticosteroid level or detectable HBV DNA in a patient with previously undetectable levels and/or reappearance of HBsAg in anti-HBc positive/HBsAg negative patients.

Microbiological analyses

The presence of SARS-CoV-2 RNA in upper respiratory specimens was determined using one of two fully automated rtRT-PCR analysers: Cobas 6800 (Roche Diagnostics, Basel, Switzerland) or Alinity m (Abbott, Chicago, IL, USA). Anti-HBc was determined using the qualitative immunoassay Elecsys Anti-HBc II (Roche Diagnostics), HBsAg using the qualitative immunoassay Vitros HBsAg (Ortho Clinical Diagnostics, Raritan, NJ, USA), and anti-HBs using Vitros anti-HBs (Ortho Clinical Diagnostics). Hepatitis B DNA viral loads were determined

using commercial quantitative real-time PCR tests: Alinity m HBV Assay (Abbott) and Xpert HBV Viral Load (Cepheid, Sunnyvale, CA, USA), with all results expressed in HBV DNA IU/ml. The lower limit of detection (LoD) for HBsAg was 0.08 IU/ml. For HBV DNA the LoD was 4.29 IU/ml and 3.2 IU/ml with Alinity m and Xpert assays, respectively. The lower limit of quantification (LoQ) of HBV DNA was 10 IU/ml with both HBV DNA assays used. All tests were conducted and results interpreted according to the manufacturers' instructions.

Statistical analysis

Categorical variables were described as frequencies (%) and numerical variables using medians with interquartile ranges (IQR). Differences among the studied groups were examined with two-tailed Pearson's Chi-squared or Fisher's exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables. *P*-value of less than 0.05 were considered statistically significant and used for descriptive purposes. The association between anti-HBc positivity and progression to critically severe disease, controlling for a set of covariates expected to influence the outcome (age, sex, Charlson comorbidity index, and vaccination status), was estimated using multiple logistic regression. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). R programming language was used for statistical analyses [10].

Results

Characteristics of hospitalised patients with COVID-19

Out of 2,877 patients with PCR-confirmed SARS-CoV-2 infection during the selected study periods, 2,464 (85.6%) were hospitalised for COVID-19, while 413 (14.4%) were admitted for non-COVID-19 medical conditions. At admission, hypoxemia was observed in 1,938 out of 2,464 (78.7%) COVID-19 patients and developed after admission in an additional 198 patients. Corticosteroids were administered to 2,136/2,464 (86.7%) hospitalised COVID-19 patients with hypoxemia; among them, 1,364 (63.9%) received dexamethasone, 411 (19.2%) high dose methylprednisolone, and 361 (16.9%) high dose methylprednisolone after initially receiving dexamethasone due to a worsening respiratory condition. Compared to patients treated solely with dexamethasone, those who received methylprednisolone alone or after initially receiving dexamethasone progressed to critically severe disease more often (417/772; 54.0% vs. 185/1,364; 13.6%; $p < 0.001$).

Compliance with institutional recommendations for HBV testing

Anti-HBc screening was conducted for 1,793 out of 2,136 (83.9%) hospitalised COVID-19 patients treated with corticosteroids (Fig. 1). Compliance with screening decreased over time (Table 1). Patients who underwent anti-HBc screening tended to be younger and less frequently lived in long-term care facilities. They also presented less often with critically severe disease or died and were more regularly prescribed methylprednisolone compared to those who were not screened (Table 1). Among the 1,793 patients screened for anti-HBc, 157 (8.8%) tested positive, and five (0.3%) were also HBsAg positive. Basic characteristics of patients according to their anti-HBc status are presented in Table 2. Reflex testing for HBsAg was performed for all the 157 anti-HBc positive patients (100%), while anti-HBs testing was conducted for all except one patient (99.4%). HBV DNA testing was done for all five patients who were HBsAg-positive. Notably, in univariate analysis, anti-HBc positive patients exhibited a greater likelihood of progressing to critical COVID-19 and death compared to their anti-HBc negative counterparts (59/157; 37.6% vs. 409/1636; 25.0%; $p < 0.001$). After adjusting for age, sex, comorbidities, and vaccination status in multivariate analysis, anti-HBc positive patients had higher odds for progression to critical illness or death (Table 3).

Characteristics of HBsAg positive patients

Chronic HBV infection was known upon admission for three patients. Two of them were on long-term tenofovir treatment, while a third had no indication for HBV therapy. All were aviremic (HBV DNA negative/below LoD) and none were diagnosed with liver cirrhosis upon admission. One HBsAg positive patient on anti-HBV treatment succumbed to COVID-19 pneumonia, while HBV DNA was not detected at the end of corticosteroid treatment (one received only dexamethasone and one received dexamethasone and high dose methylprednisolone) or 12 months later in the other two initially positive HBsAg patients. The fourth HBsAg positive patient was diagnosed with HBV infection *de novo*, and prophylactic treatment with entecavir was started after four days of dexamethasone, initiated upon admission. He progressed to severe COVID-19, was mechanically ventilated and corticosteroid therapy was transitioned to high dose methylprednisolone on the 12th day after admission to hospital. His transaminase levels rose to maximum three times the upper limit of normal (ULN) on the seventh day after introducing corticosteroids and declined afterwards. The patient's HBV DNA remained below 10 IU/ml at follow-up four-months after hospitalisation and was undetectable at the 12-month follow-up. The fifth HBsAg positive patient also received a *de novo* diagnosis of HBV infection. On admission, HBsAg titres were not quantified. High-dose methylprednisolone for COVID-19 pneumonia was given (1 mg/kg daily for 7 days followed by tapering over two weeks), but antiviral prophylaxis was not started. He had detectable HBV viremia, but

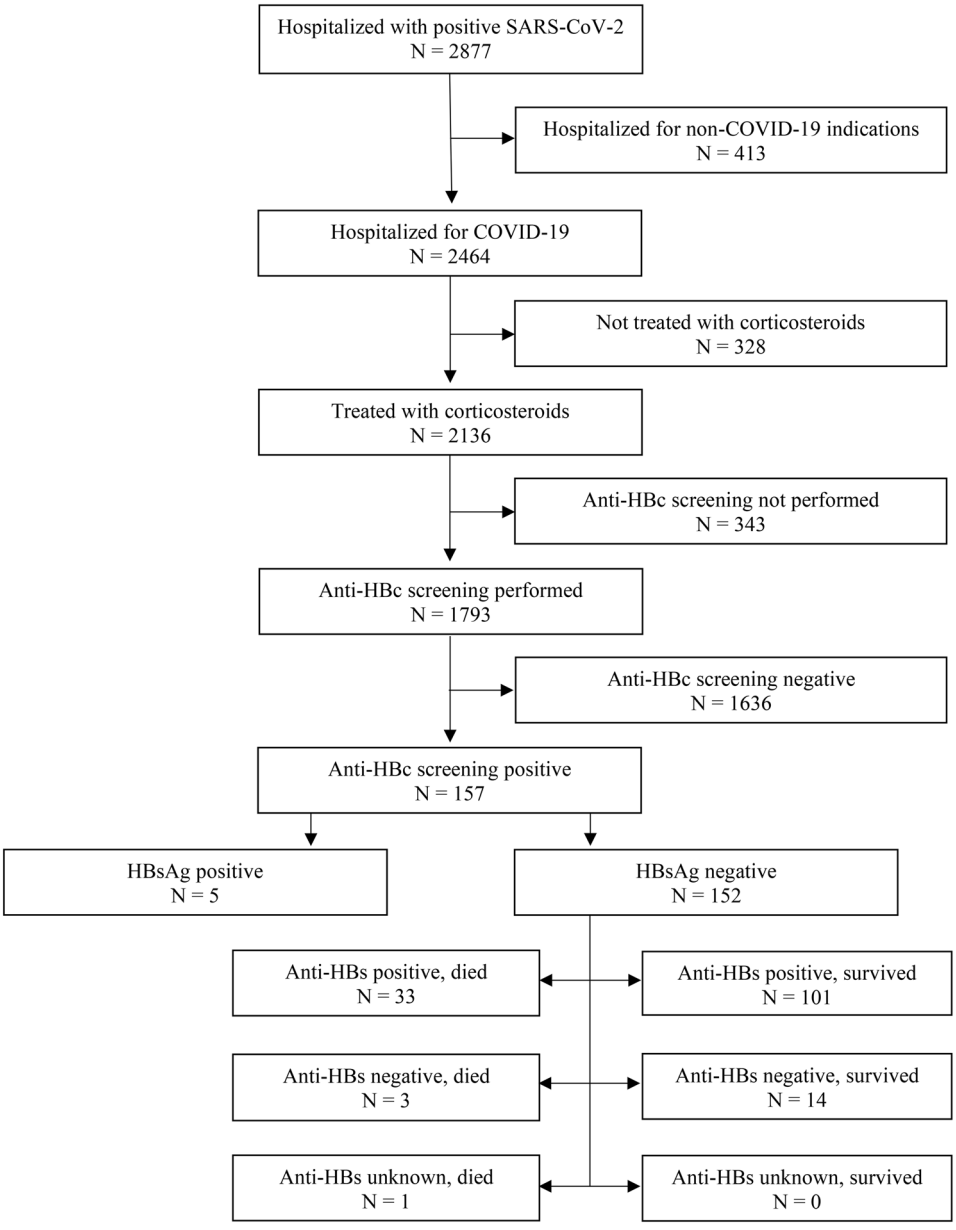

Fig. 1 Flow diagram

below lower limit of quantification (HBV DNA < 10 IU/ml) at admission and at hospital discharge, 14 days later. On admission, he had normal liver tests, but his transaminase levels increased to 2.4 ULN during hospitalisation and returned to normal six weeks later. At two-year follow-up, he displayed normal liver test results, low serum HBV DNA (31 IU/ml), and low serum HBsAg (12.9 IU/ml). He was subsequently released from further follow-up due to resolved HBV infection and advanced age. No HBsAg positive patients were coinfected with HDV, HIV or HCV.

Characteristics of anti-HBc positive/HBsAg negative patients

Among the 152 anti-HBc positive/HBsAg negative patients, 112 were anti-HBs positive (63/112; 56.3% had anti-HBs titres ≥ 100 IU/L), while 39 had isolated positive anti-HBc serologies. The anti-HBs status remained undetermined for one anti-HBc positive/HBsAg negative patient. Reflex testing for HBV DNA was not performed in these patients. Patients' characteristics according to the prescribed corticosteroid therapy are presented in Table 4. Thirty-seven (24.3%) of the anti-HBc positive/HBsAg negative patients died during hospitalisation due to COVID-19 or related medical complications. Notably,

Table 1 Characteristics of the 2136 hospitalised patients treated with corticosteroids for COVID-19 according to whether anti-HBc screening was performed or not

Characteristic	Anti-HBc screened *N* = 1793 (84.0)	Anti-HBc not screened *N* = 343 (16.0)	*p* value[a]
Age in years	70 (59–79)	78 (65–86)	**< 0.001**
Men	1082 (60.3)	177 (51.9)	**0.003**
Resident of a long-term care facility	146 (8.1)	80 (23.3)	**< 0.001**
Charlson comorbidity index	3.0 (2.0–5.0)	4.0 (2.0–6.0)	**0.006**
Immunocompromised[b]	66 (3.7)	10 (2.9)	0.385
Liver cirrhosis	16 (0.9)	0 (0)	0.092
Hypoxemic at admission	1501 (83.7)	291 (84.8)	0.603
Screening period[c]	1120 (60.5)	161 (46.9)	**< 0.001**
Wild-type	425 (23.7)	89 (25.9)	
Delta	248 (13.8)	93 (27.1)	
Omicron			
Corticosteroids	1117 (62.3)	247 (72.0)	**< 0.001**
Dexamethasone	347 (19.4)	64 (18.7)	
Methylprednisolone	329 (18.3)[d]	32 (9.3)[d]	
Both			
Critically severe disease (WHO score 7–10)	469 (26.2)	134 (39.1)	**< 0.001**
Died (WHO score 10)	263 (14.7)	109 (31.8)	**< 0.001**
Duration of hospital stay in days	12 (7–21)	9 (5–19)	**< 0.001**

Data are n (%) or median (95% confidence interval). *WHO* World Health Organization [8]

[a]Bold values indicate statistically significant results

[b]Patients with immunocompromising conditions and treatments: active treatment for solid tumour ($n = 27$), hematologic malignancy ($n = 18$), receipt of solid organ transplant ($n = 14$), treatment with B-cell depleting agents ($n = 7$) or antimetabolites ($n = 5$), post-splenectomy ($n = 3$), receipt of hematopoietic cell transplant ($n = 1$), and primary immunodeficiency ($n = 1$)

[c]SARS-CoV-2 wild-type predominant period (from November 1, 2020, to March 31, 2021); Delta predominant period (from October 1 to November 23, 2021; Omicron predominant period (from January 15 to April 8, 2022)

[d]Number of patients who received methylprednisolone 1 mg/kg daily for seven days followed by tapering after first receiving dexamethasone 6 mg daily or an equivalent dose of other corticosteroids for up to 10 days

Table 2 Characteristics of the 1793 anti-HBc screened hospitalised patients treated with corticosteroids for COVID-19 according to anti-HBc positivity status

Characteristic	Anti-HBc positive *N* = 157 (8.8)	Anti-HBc negative *N* = 1636 (91.2)	*p* value[a]
Age in years	70 (63–79)	70 (59–79)	0.353
Men	96 (61.1)	986 (60.3)	0.830
Born outside Slovenia[b]	70 (44.6)	288 (17.6)	**< 0.001**
Resident of long-term care facility	11 (7.0)	135 (8.3)	0.586
Charlson comorbidity index	4.0 (2.0–5.0)	3.0 (2.0–5.0)	0.183
Vaccinated against COVID-19	21 (13.4)	257 (15.7)	0.440
Hypoxemic at admission	128 (81.5)	1373 (83.9)	0.437
Corticosteroid	89 (56.7)	1028 (62.8)	**0.049**
Dexamethasone	42 (26.8)	305 (18.6)	
Methylprednisolone	26 (16.6)[b]	303 (18.5)[b]	
Both			
Remdesivir	48 (30.6)	470 (28.7)	0.626
Critically severe disease (WHO score 7–10)	59 (37.6)	409 (25.0)	**< 0.001**
Died (WHO score 10)	38 (24.2)	225 (13.8)	**< 0.001**
Duration of hospital stay in days	12 (7–22)	12 (7–21)	0.733

Data are n (%) or median (95% confidence interval). *WHO* World Health Organization [8]

[a]Bold values indicate statistically significant results

[b]Born in countries of ex-Yugoslavia or Eastern Europe

[c]Number of patients who received methylprednisolone 1 mg/kg daily for seven days followed by tapering after first receiving dexamethasone 6 mg daily or an equivalent dose of other corticosteroids for up to 10 days

Table 3 Association between anti-HBc positivity and progression to critically severe disease (the world health organization COVID-19 clinical progression scale 7–10) [8]

Characteristic	Odds ratio (95% CI)	*p* value[a]
Anti-HBc status (positive vs. negative)	1.80 (1.27–2.54)	**< 0.001**
Age in years	1.02 (1.01–1.03)	**0.004**
Sex (male vs. female)	1.33 (1.06–1.66)	**0.014**
Charlson comorbidity index	1.11 (1.04–1.18)	**0.001**
Vaccination status against COVID-19 (vaccinated vs. unvaccinated)	0.59 (0.43–0.81)	**0.001**

CI confidence interval

[a]Bold values indicate statistically significant results

Table 4 Characteristics of HBsAg negative/anti-HBc positive patients hospitalised for COVID-19 according to corticosteroid therapy

Characteristic	Dexamethasone only *N* = 87 (57.2)[a]	Methylprednisolone *N* = 65 (43.3)[b]	*p* value[c]
Age in years	71 (65–81.5)	69 (61–74)	0.091
Men	46 (52.9)	46 (70.8)	0.026
Resident of long-term care facility	6 (6.9%)	3 (4.6)	0.733
Charlson comorbidity index	4.0 (2.0–5.0)	4.0 (2.0–4.0)	0.411
Vaccinated against COVID-19[d]	13 (14.9)	8 (12.3)	0.641
Hypoxemic at admission	61 (70.1)	62 (95.4)	**< 0.001**
Critically severe disease (WHO score 7–10)	12 (13.8)	44 (67.7)	**< 0.001**
Died (WHO score 10)	11 (12.6)	26 (40.0)	**< 0.001**

Data are n (%) or median (95% confidence interval). *WHO* World Health Organization [8]

[a]Dexamethasone 6 mg daily or an equivalent dose of other corticosteroids for up to 10 days

[b]Methylprednisolone 1 mg/kg daily for seven days followed by tapering. Out of 65 patients, 24 patients received methylprednisolone after first receiving dexamethasone because of deteriorating respiratory status

[c]Bold values indicate statistically significant results

[d]Patients receiving the second dose of BNT162b2, mRNA-1273, or ChAdOx-1 S or the first dose of Ad.26.COV2.S at least 14 days before symptom onset

none of the deceased patients exhibited signs of HBV reactivation or hepatopathy of unknown origin. Furthermore, none of the 115 out of 152 (75.7%) anti-HBc positive/HBsAg negative patients who survived acute COVID-19 experienced documented HBV reactivation following corticosteroid treatment.

Discussion

This retrospective observational cohort study investigated prospectively collected clinical data of 1,793 hospitalised adult patients treated with corticosteroids for COVID-19, revealing that 84% underwent HBV screening with anti-HBc testing. Among these patients, positive anti-HBc was identified in 157 (8.8%) individuals, with five (0.3%) also testing positive for HBsAg. Of the three patients with known HBsAg positivity at admission, antiviral treatment for chronic hepatitis B was maintained in two cases (one patient died from COVID-19 pneumonia), while one of the two newly identified HBsAg positive patients was initiated on antiviral treatment. Notably, there were no cases of HBV reactivation or transaminitis of unknown origin among the 152 HBsAg negative/anti-HBc positive patients, none of whom received antiviral prophylaxis.

The estimated prevalence of HBsAg in Slovenia is 0.5% [7]. A similar prevalence of 0.3% (95% CI 0.09% to 0.65%) was found in this study. Due to the heightened risk of HBV reactivation associated with certain immunosuppressive therapies, clinical guidelines recommend HBV screening before the initiation of such treatments [11–14]. In our institution, anti-HBc testing was recommended for all patients receiving corticosteroids for COVID-19, followed by reflex HBsAg testing in anti-HBc positive cases. The latest EASL guidelines additionally recommend baseline HBV DNA testing in HBsAg negative/anti-HBc positive individuals to rule out active infection [5]. Contrary to low HBV screening rates before immunosuppressive therapy in some previously published studies [15, 16], this study found that 84% of patients receiving corticosteroids for COVID-19 were tested for HBV. Screened patients were younger, less likely to reside in nursing facilities, and exhibited a better overall prognosis than those who did not undergo anti-HBc testing. Interestingly, the results highlighted a decrease in anti-HBc screening rates over the course of the pandemic (Table 1), despite guidelines for HBV screening remaining unchanged throughout this period. There are numerous complex factors contributing to clinician non-adherence to guidelines [17]. The large number of COVID-19 patients, rapidly changing standards of care and clinical presentations of COVID-19 may have played a role in these deviations.

Case reports have suggested that SARS-CoV-2 may trigger HBV reactivation independently of immunocompromising treatments, possibly through viral interactions or disruption of the immune system [18, 19]. Nonetheless, the relationship between HBV infection and COVID-19 outcomes remains inconsistent; the presence of chronic HBV infection alone does not seem to lead to a more severe course of COVID-19 in some studies. One of the larger studies conducted on hepatopathy in COVID-19, which included 5,539 patients from January 2020 to January 2021 in Hong Kong, found that acute liver injury, likely due to multiple factors, was linked to higher mortality. However, chronic HBV infection (identified in 6.3%) and resolved HBV infection (detected in 6.4%) were not associated with increased liver impairment or mortality [20]. In contrast, the present study found that anti-HBc positive patients had higher odds for progression to

critically severe COVID-19. This association remained significant after adjusting the analysis for potential confounders. These results are consistent with recent data from a nationwide study from Sweden, in which chronic HBV infection was associated with severe COVID-19 (adjusted OR 1.242, 95% CI 1.097–1.403) [21].

In the first year of the pandemic, the EASL recommended considering the introduction of antiviral treatment for patients with active chronic HBV as well as occult HBV infection who were receiving corticosteroids or other immunosuppressive drugs for COVID-19. This recommendation resulted from the uncertainty surrounding the risk of HBV reactivation under these conditions [56]. A knowledge gap persists on how COVID-19 and systemic corticosteroids used for treating COVID-19 affect the course of HBV because HBV testing is not always performed. HBV reactivation can occur from two weeks to two years after the initiation of immunosuppressive therapy with increased risk continuing after completion of treatment, depending on HBV infection status, other comorbidities, and the type of immunosuppressive therapy used [4, 22]. Indeed, the long-lasting immune-suppressive effects of anti-CD20 therapies, not used to treat COVID-19 infections, require careful vigilance for HBV reactivation long after discontinuation of therapy. Steroids are not known to have such long-lasting immune effects after discontinuation. Any late HBV reactivations, beyond the follow up period of this study, might be due to other undocumented causes rather than the short course of corticosteroids. It has been estimated that HBsAg positive patients are five to eight times more likely to experience HBV reactivation during immunosuppressive therapy compared to HBsAg negative/anti-HBc positive patients [13]. Furthermore, the risk of HBV reactivation for HBsAg negative/anti-HBc positive individuals undergoing immunosuppressive therapy may be influenced by the level of anti-HBc antibodies [5]. Much of the literature concerning HBV reactivation in immunocompromised hosts relates to rheumatologic, oncologic, and immune-mediated conditions. Cumulative exposure to immunosuppressive agents in these cases differs significantly from the short courses used in COVID-19 patients who often receive high-dose systemic corticosteroids for no more than 10 days. The daily dose of corticosteroid appears to be more important than the duration of corticosteroid treatment as a risk for HBV reactivation. Daily doses equivalent to 20–40 mg of prednisone or 6 mg dexamethasone were associated with intermediate to high risk (5.7% to 14.8%) of reactivation (defined as alanine aminotransferase > 2x ULN at one year) in two retrospective studies of 5254 and 1800 anti-HBc positive patients conducted in Hong Kong from 2001 to 2004 and from 2001 to 2010, respectively [23, 24].

Furthermore, the gravity of reactivation is an important factor to consider. A prospective cohort study showed that HBsAg negative/anti-HBc positive COVID-19 patients treated with various combinations of immunosuppressive therapies and high-dose corticosteroids not receiving an antiviral agent appeared to have a low risk of reactivation at 1–2 months post COVID-19 treatment. Only 2/23 patients without prophylaxis were known to have detected HBV DNA, but below the limits of quantification and neither patient had an elevated ALT [25]. A prospective observational cohort study reported HBV reactivation in 3 of 15 HBsAg negative/anti-HBc positive patients (20%) within 3 months after short courses of immunosuppressive therapy for COVID-19. However, HBV viral loads were ≤ 10 IU/ml and there was no accompanying transaminitis. No case required antiviral therapy [26]. Another prospective observational cohort study of 54 HBsAg negative/anti-HBc positive COVID-19 patients suggested that HBV reactivation after receipt of baricitinib or tocilizumab and dexamethasone 6 mg daily for up to 10 days was low with no sero-reversions noted and normalization of transaminitis at up to 24 weeks without antiviral prophylaxis. However, no virologic monitoring was performed and there was significant loss to follow up [27]. In a retrospective observational study with 84 anti-HBc positive patients not treated with antiviral prophylaxis hospitalised with SARS-CoV-2 (18 HBsAg positive, 41 HBsAg negative/anti-HBs positive, and 25 HBsAg negative/anti-HBs negative), 10.7% had an increase in ALT. Steroid treatment in 58.3% was a risk factor for transaminitis. No seroreversion or significant transaminitis was noted and antiviral treatment was not instituted in the patients. Transaminitis levels normalized after resolution of COVID-19 further obfuscating the etiology of transaminitis. A less than 1 log increase in HBV DNA was seen in two HBsAg positive patients and two anti-HBc positive/anti-HBs negative patients with a decrease of HBV viremia to baseline at 3 months of follow-up [28]. In a Spanish study of 61 HBsAg negative/anti-HBc positive COVID-19 patients, 25 (41%) received corticosteroids alone or with other immunomodulators [25]. None of 9 without prophylaxis developed HBsAg seroreversion and low HBV viremia (HBV DNA < 10 IU/ml) without transaminitis was detected in only one. Results of the present study are in line with these previous studies.

This study has several limitations. Firstly, it was observational, so the influence of confounding variables cannot be ruled out, particularly those that may have affected physicians' decisions to screen for HBV. However, several relevant factors were considered, including age and the patients' baseline health status. Secondly, since the study was limited to hospitalised patients, the incidence of HBV infection or the impact of COVID-19 on the

course of HBV in the outpatient population cannot be assessed. This last aspect is less critical since outpatients with mild COVID-19 typically do not receive corticosteroids for treatment. Thirdly, the study was conducted at a single institution in a relatively small region of Central Europe with low ethnic diversity and few HBsAg positive patients, reducing generalizability. Fourthly, patients who were not screened for HBV and therefore excluded from the analysis had higher mortality rates than those who were screened. Although mortality in this subgroup was due to respiratory pathology without hepatic failure, it remains unclear how the inclusion of these patients through HBV screening might have influenced our results. The strength of this study is that most of the patients analysed were screened for HBV, enabling us to determine the prevalence of HBV infection and assess the risk of HBV reactivation in a cohort of COVID-19 patients receiving corticosteroid therapy. This information is vital for decision-making regarding HBV screening strategies and the use of antiviral prophylaxis.

Conclusions

Relatively high rates of anti-HBc positivity in an otherwise HBV low prevalence country such as Slovenia justify universal HBV screening in patients receiving immunosuppressive therapy. In the studied cohort of hospitalised adults, few COVID-19 cases treated with corticosteroids required pharmaceutical intervention for HBV infection. The results suggest that the probability of HBV reactivation in patients with occult or resolved HBV who receive short courses of corticosteroids for COVID-19 is low. Future studies should consider stratifying the risk of HBV reactivation in COVID-19 patients based on HBV status and type of immunosuppressive therapy.

Abbreviations

COVID-19	Coronavirus disease 2019
HBV	Hepatitis B
EASL	European Association for the Study of the Liver
IQR	Interquartile range
OR	Odds ratio
CI	Confidence interval

Acknowledgements

We would like to thank all health-care professionals and laboratory personnel involved in managing patients with COVID-19 at the University Medical Centre in Ljubljana, Slovenia.

Author contributions

D.S. is the lead and corresponding author. D.S. conceptualized and designed the study, participated in data acquisition and interpretation, searched the literature, and drafted the manuscript. S.C.-A. participated in data interpretation, literature search, and drafting the manuscript. N.K. participated in data interpretation and performed the statistical analyses. J.J.G. and D.J. participated in data acquisition and interpretation. M.P. and T.Š. participated in data acquisition and interpretation, performed laboratory analyses and provided expertise in interpreting microbiological data. All the authors approved the final version for publication. All authors have read and agreed to the published version of the manuscript.

Funding

This research was supported by the Slovenian Research Agency (grant number P3-0154) and the University Medical Centre Ljubljana, Slovenia (TP20220153).

Data availability

The anonymous data generated or analysed during this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The research was conducted according to the guidelines of the Declaration of Helsinki and approved by the Medical Ethics Committee of the Ministry of Health of the Republic of Slovenia (No. 0120–500/2020/3 and 0120–343/2021-2711-25) and retrospectively registered with ClinicalTrials.gov, NCT07154212, September 2, 2025. This was an observational study, and the need for consent to participate was waived by the Medical Ethics Committee of the Ministry of Health of the Republic of Slovenia.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 17 September 2025 / Accepted: 13 January 2026
Published online: 20 January 2026

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